FICHE PROJET EUROPEEN			
ACRONYME : PAToolBox			
NOM COMPLET DU PROJET	Synthèse des acides phosphatidiques analogues cliquables et en cage		
NUMERO DE CONVENTION	19P02931 / 19E00838		
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SITE INTERNET DU LABORATOIRE ET PROJET			
DESCRIPTION DU PROJET			
RESUME	Phosphatidic acids (PAs) are the simplest phospholipids naturally present in all living organisms and have attracted considerable attention being both lipid second messengers and modulators of membrane shape. In consequence, PAs have been proposed to play pivotal roles for various cellular functions and accordingly abnormalities in PA producing enzymes occur in numerous diseases including neurodegeneration, intellectual disabilities, cancer, and hypertension. At the molecular level, PAs interact with various proteins and are predicted to modify membrane topology, but very limited information regarding the kinetics of these interactions and structural effects is available due to the lack of adequate tools. Most of the tools that we propose to develop will bear a small biorthogonal chemical function and photoactivatable components that will be useful to study in a time and space dependent manner, living cells or organisms. These tools will thus enable us and our partners to address simultaneously two topics that recently boosted the progresses in the study of living organisms: photopharmacology and in cellulo chemistry.		

OBJECTIFS	Our approach to manipulate PA levels and study their dynamics is the direct addition of membrane permeable PA analogues. Relying on the know-how of Pr. Renard's team in fluorescence, organophosphorus chemistry and click chemistry, PA analogues with a caged-phosphate head group that can be uncaged after UV illumination (see P. Klan et al. Chem. Rev. 2013. 113, 119-191) will be synthesized in vitro. A small bioorthogonal clickable moiety (azide or methylcyclopropene) will be incorporated on the glycerol head in order to graft, through click chemistry (through CuAAC, SPAAC or iEDDA, see M. King and A. Wagner Bioconjugate Chem., 2014, 25, 82583 or Boutureira, et al. Chem. Rev. 2015. 115, 2174-95), in vitro or in cellulo, a fluorescent reporter or a photo-crosslinker (see P Kleinner et al. Angew. Chem. Int Ed. 2017, 56 1396-1401) reactive group. We must emphasize that we propose to focus on caging the head-group, and modifiying the glycerol head instead of the fatty acids since we specifically want to determine the function of the different forms of PAs, thus maintaining the fatty acids untouched is crucial.
IMPACTS ATTENDUS ET FINALITE	At a first level this multidisciplinary project constitutes a real challenge that will contribute to unravel the complexity of lipid function in membrane trafficking and fusion and will undoubtedly benefit from the respective specific expertise of the three partners. A first common project was submitted to ANR in 2018, which was well evaluated, the main weak point that has been raised is the lack of preliminary results on the photoactivatable probes which were proposed in this submission, and the lack of experience of the chemical team in the field. This project thus aims at answering these weak points by providing a proof of concept and a preliminary experience of the chemistry team in photopharmacology and in cellulo chemistry. A successful application to this ANR call would be a first expected impact for this project as well as the involvement of the bioorganic chemistry team in international research programs such as H2020 or ITN programs. At a second level several aspects of the project could provide (i) directions to envision novel targeted therapies to a wide range of pathologies related to a dysfunction of neurosecretion, but also membrane trafficking defects at large and (ii) novel biocompatible chemical tools to study all kind of lipid-protein interactions that could be crucial in any relevant physiological function in living cells, keeping the fatty acid side chains untouched, widening the strategy to other lipids than PAs. At a third level, since phospholipids are key elements of cellular signaling pathways, it is reasonable to expect significant benefits in the fields of health.
RESULTATS	
MODALITES DE FINANCEMENT	BUDGET TOTAL : 150000€
Niveau de soutien FEDER / FSE / FAEDER	75000€
Niveau de soutien région	75000€
Nb de personnes affectées à l'opération	2
L'Europe s'engage en Normandie avec le Fonds Européen de Développement Régional	